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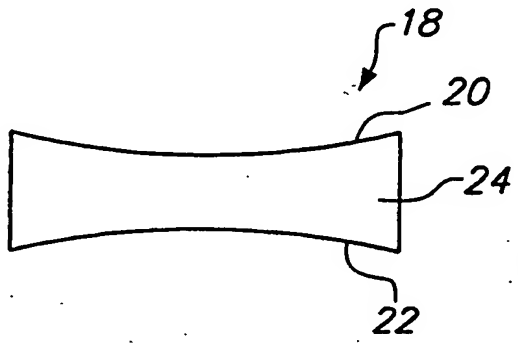
(54) Title: DRUG DOSAGE UNIT FOR BUCCAL ADMINISTRATION OF STEROIDAL ACTIVE AGENTS

(57) Abstract

A buccal dosage unit (2) is provided for administering a combination of steroidal active agents to a female individual. The novel buccal drug delivery systems may be used in female hormone replacement therapy, in female contraception, to treat female sexual dysfunction, and to treat or prevent a variety of conditions and disorders which are responsive to the active agents discussed herein. The buccal dosage unit (2) comprises a progestin, an estrogen and optionally an androgenic agent, as well as a polymeric carrier that bioerodes and provides for delivery of the active agents throughout a predetermined drug delivery period.



DRUG DOSAGE UNIT FOR BUCCAL ADMINISTRATION OF STEROIDAL ACTIVE AGENTS

TECHNICAL FIELD

This invention relates generally to pharmaceutical compositions and methods for administering pharmacologically active agents. More particularly, the invention relates to buccal drug delivery, and to a buccal dosage unit and method for administering a combination of steroidal active agents, e.g., for female hormone replacement therapy, female contraception, treatment of female sexual dysfunction, and the like.

BACKGROUND ART

Androgens are the hormones that cause most of the masculinizing changes that occur in males during puberty. *Harrison's Principles of Internal Medicine*, 12th Edition (New York, NY: McGraw Hill, Inc., 1991). However, low levels of androgens are also present in normal females. Testosterone and other androgens are secreted by the ovary and the adrenal cortex. *See, e.g.*, Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, 9th Edition (New York, NY: McGraw Hill, Inc., 1996). Dehydroepiandrosterone (DHEA) and androstenedione are also synthesized by both the adrenal gland and the ovary and can be converted to testosterone or estrogen in peripheral tissues. The daily rate of production of testosterone in women is on the order of 0.25 mg, about half of which is derived from the metabolic conversion of androstenedione to testosterone at extraglandular sites. The plasma concentration of testosterone in women alters with the menstrual cycle and ranges from 15 to 65 nanogram/deciliter (ng/dl). As with estrogen, testosterone levels peak at the preovulatory and luteal phases of the cycle. At menopause, plasma androgen and estrogen levels are reduced but not completely absent in women. Alteration in the hormone profile is believed to be an underlying cause of menopausal symptoms in women, including vasomotor instability ("hot flash"), atrophy of the urogenital epithelium and skin, decreased size of the breasts and osteoporosis. *See, e.g., Harrison's Principles of Internal Medicine, supra.*

Alteration in normal hormonal levels can also cause sexual dysfunction. For example, estrogen deficiency, causing vaginal atrophy and dyspareunia, is a common cause of sexual

the "first pass" effect in the liver encountered with oral formulations, and enables the use of smaller doses of active agents (and thus avoids the side effects associated with conventional formulations). In addition, when an androgenic agent is included, as in the preferred embodiment herein, essentially complete hormone replacement is provided. That is, with respect to the latter point, estrogen/progestin therapies do not in fact provide "replacement" of the complete hormone profile of the premenopausal woman, because, as discussed above, androgens are also present in premenopausal women. In a preferred embodiment, then, the present invention calls for one or more androgenic agents to be administered along with a progestin and an estrogen.

The method and compositions of the invention may also be used to treat other conditions for which the disclosed hormone combination is useful. For example, the novel drug dosage units can be used to treat female sexual dysfunction, to effect female contraception, to improve vaginal muscle tone and tissue health, and to enhance vaginal lubrication.

Drug therapy for treating female sexual dysfunction has been described. For example, U.S. Patent No. 4,507,323 to Stern describes the use of the anxiolytic *m*-chloro-α-*t*-butylamino-propiophenone in the treatment of sexual dysfunction in male and female individuals. Pharmaceutical compositions containing the agent are described, which are presented in discrete units, e.g., cachets, tablets, capsules. ampules and suppositories for oral or anal delivery of the agent. Additionally, U.S. Patent No. 4,521,421 to Foreman describes the treatment of sexual dysfunction in male and female individuals using the stereoisomers of octahydro-pyrimidoquinoline agents. centrally acting dopamine agonists. U.S. Patent No. 5,190,967 to Riley describes the treatment of sexual disorders in male and female individuals using heterocyclic benzodioxinopyrrole compounds. which, like the drugs described in the aforementioned patents, are centrally acting agents.

Drug therapy involving buccal administration of steroid hormones has also been described. For example, U.S. Patent No. 4,755,386 to Hsiao et al. generally describes the buccal administration of various medicaments. including estrogens. progestins and androgens; combinations of the medicaments. however. are not contemplated. Furthermore, the buccal tablets of Hsiao et al., weighing on the order of 50 mg. contain adhesive. disintegrant and excipient in addition to the active agent. with the inactive ingredients representing up to about

It is yet another object of the invention to provide female hormone replacement therapy by buccally administering a pharmaceutical composition as described herein to a woman in need of such therapy.

It is a further object of the invention to provide a method for effecting contraception in a fertile mammalian female by buccally administering a pharmaceutical composition as described herein.

It is still a further object of the invention to treat female sexual dysfunction by buccally administering a combination of active agents as described herein to a woman in need of such treatment.

It is an additional object of the invention to provide methods for improving vaginal muscle tone and tissue health and for enhancing vaginal lubrication, each of such methods involving buccal administration of a pharmaceutical composition as described herein to a woman in need of such treatment.

Additional objects, advantages and novel features of the invention will be set forth in part in the description which follows, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention.

Accordingly, in a first embodiment, a pharmaceutical composition is provided in the form of a simple, compact buccal dosage unit comprising therapeutically effective amounts of an androgenic agent, a progestin and an estrogen, or therapeutically effective amounts of an estrogen and a progestin, in a bioerodible polymeric carrier, wherein the carrier is such that it enables the dosage unit to adhere to the buccal mucosa. Following application to the buccal mucosa, gradual and complete erosion of the unit occurs over a predetermined time period, thus providing drug delivery throughout that time period. In a preferred embodiment, the dosage unit contains only the active agents to be administered and the polymeric carrier. However, other components, particularly a lubricant, may be incorporated to facilitate manufacture of the unit or if otherwise found to be necessary or desirable. The buccal dosage units are typically far smaller than conventional buccal delivery systems--the present tablets are on the order of 5-20 mg, typically 10-15 mg--and do not require a plurality of excipients, disintegrants, adhesives, or the like, nor are fragrances or permeation enhancers necessary. Accordingly, the novel dosage units are more comfortable than conventional systems because of their compact size. The novel units are also highly effective in providing therapeutically

Figure 2 schematically illustrates an alternative and preferred embodiment of a buccal dosage unit according to the invention.

Figure 3 schematically illustrates a second alternative embodiment of a buccal dosage unit according to the invention.

Figure 4 illustrates the placement of the buccal dosage unit in the preferred location in the oral cavity.

MODES FOR CARRYING OUT THE INVENTION

Before describing the present invention in detail, it is to be understood that this invention is not limited to specific active agents or carriers as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

It must be noted that, as used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an estrogen" or "an estrogenic agent" includes a mixture of two or more such active agents, reference to "a buccal permeation enhancer" includes mixtures of two or more enhancers, reference to "a carrier" or "an excipient" includes a combination of two or more such materials, and the like.

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

The terms "drug" or "pharmacologically active agent" or "active agent" are used interchangeably herein to refer to a compound or composition of matter which, when administered to an organism (human or animal) induces a desired pharmacologic and/or physiologic effect by local and/or systemic action. The active agents herein are steroid hormones, including androgenic agents, e.g., testosterone and derivatives, analogs, esters and salts thereof, progestins (also referred to herein and in the art as "progestogens"), e.g., progesterone and the like, and estrogens, e.g., ethynyl estradiol and the like.

By "buccal" drug delivery is meant delivery of a drug by passage of a drug through the buccal mucosa into the bloodstream. Preferably, buccal drug delivery is effected herein by placing the buccal dosage unit on the upper gum or opposing inner lip area of the individual undergoing drug therapy.

the term "treating" is used herein, encompasses both prevention of female sexual dysfunction and treatment of the dysfunction in a clinically symptomatic individual.

In one embodiment, then, a pharmaceutical composition is provided in the form of a buccal dosage unit for the administration of a combination of steroidal agents. The dosage unit comprises (a) therapeutically effective amounts of an androgenic agent, a progestin and an estrogen, or of a progestin and an estrogen, and (b) a bioerodible polymeric carrier as will be described in detail below. The dosage unit is fabricated so as to erode gradually over a predetermined time period, wherein drug delivery is provided essentially throughout. The time period is typically in the range of 8 hours to 24 hours; that is, for an 8-hour unit, erosion will occur throughout an 8-hour period and be substantially complete at the 8-hour point, while for a 24-hour unit, erosion will occur throughout a 24-hour period and be substantially complete at the 24-hour point. The buccal dosage unit may further comprise a lubricant to facilitate manufacture, e.g., magnesium stearate or the like. Additional components that may be included in the buccal dosage unit, but are neither required nor preferred, are flavorings, permeation enhancers, diluents, binders, and the like. As a buccal drug delivery system, the novel dosage unit avoids the disadvantages encountered with oral drug administration, e.g., degradation of the agents by fluids present in the gastrointestinal tract and/or first-pass inactivation in the liver. In addition, because of its compact size, the unit is not associated with the discomfort encountered with larger, conventional buccal drug delivery systems. Also, the units are convenient in that the wearer need change the unit only once or twice daily, i.e., with 24-hour or 12-hour systems, respectively; a 12-hour unit to be applied once in the morning and once in the evening is optimal. Finally, because of the compositional simplicity of the unit--in a preferred embodiment, the unit contains only the active agents and the polymeric carrier--manufacture of the dosage form is straightforward and economical.

The buccal dosage units of the invention are useful in providing effective female hormone replacement therapy, in that the occurrence of symptoms or conditions resulting from altered hormone levels is mitigated or substantially prevented. The invention is thus useful to treat women for whom ovarian steroid production has been altered, either because of menopause; surgical or radiation treatment, ovarian ablation, or premature ovarian failure. As noted elsewhere herein, the invention is also useful to treat female sexual dysfunction, to effect female contraception, to improve vaginal muscle tone and tissue health, and for

benzoate; estriol and estriol succinate; polyestrol phosphate; estrone and its esters and derivatives, including estrone acetate, estrone sulfate, and piperazine estrone sulfate; quinestrol; mestranol; and conjugated equine estrogens. Estradiol and ethynylestradiol are particularly preferred synthetic estrogenic agents for use in conjunction with the present invention.

Suitable progestins for use in the buccal drug delivery units of the invention include, but are not limited to, acetoxypregnenolone, allylestrenol, anagestone acetate, chlormadinone acetate, cyproterone, cyproterone acetate, desogestrel, dihydrogesterone, dimethisterone, ethisterone (17α-ethynyltestosterone), ethynodiol diacetate, flurogestone acetate, gestadene, hydroxyprogesterone, hydroxyprogesterone acetate, hydroxyprogesterone caproate, hydroxymethylprogesterone, hydroxymethylprogesterone acetate, 3-ketodesogestrel, levonorgestrel, lynestrenol, medrogestone, medroxyprogesterone acetate, megestrol, megestrol acetate, melengestrol acetate, norethindrone, norethindrone acetate, norethisterone, norethisterone acetate, norethynodrel, norgestimate, norgestrel, norgestrienone, normethisterone, and progesterone. Progesterone, cyproterone acetate, norethindrone, norethindrone acetate and levonorgestrel are preferred progestins.

The aforementioned steroidal agents are selected from the group consisting of naturally occurring steroids, synthetic steroids, and derivatives thereof. The active agents may be incorporated into the present dosage units and thus administered in the form of a pharmaceutically acceptable derivative, analog, ester or salt, or the agents may be modified by appending one or more appropriate functionalities to enhance selected biological properties such as penetration through the mucosal tissue. In general, when the buccal dosage units are used to administer androgenic agents, esters are preferred relative to salts or other derivatives. Preparation of esters involves functionalization of hydroxyl and/or carboxyl groups that may be present, as will be appreciated by those skilled in the arts of pharmaceutical chemistry and drug delivery. Esters can be reconverted to the free acids, if desired, by using conventional hydrogenolysis or hydrolysis procedures.

To administer any one of the active agents in salt form, suitable pharmaceutically acceptable salts can be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry and described, for example, by J. March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 4th Ed. (New York: Wiley-Interscience,

predetermined rate upon contact with moisture. The polymeric carrier is preferably sticky when moist, but not when dry, for convenience in handling. Generally, it is preferred that the weight average molecular weight (M_w) of the polymer be in the range of approximately 4,000 to 1,000,000, more preferably in the range of approximately 100,000 to 1,000,000. One of skill in the art will appreciate that the higher the molecular weight of the polymer, the slower the erosion time.

Any polymeric carriers can be used that are pharmaceutically acceptable, provide both a suitable degree of adhesion and the desired drug release profile, and are compatible with the agents to be administered and any other components that may be present in the buccal dosage unit. Generally, the polymeric carriers comprise hydrophilic (water-soluble and water-swellable) polymers that adhere to the wet surface of the buccal mucosa. Examples of polymeric carriers useful herein include acrylic acid polymers and copolymers, e.g., those known as "carbomers" (Carbopol®, which may be obtained from B.F. Goodrich, is one such polymer). Other suitable polymers include, but are not limited to: hydrolyzed polyvinylalcohol; polyethylene oxides (e.g., Sentry Polyox® water soluble resins, available from Union Carbide); polyacrylates (e.g., Gantrez®, which may be obtained from GAF); vinyl polymers and copolymers; polyvinylpyrrolidone; dextran; guar gum; pectins; starches; and cellulosic polymers such as hydroxypropyl methylcellulose (e.g., Methocel®, which may be obtained from the Dow Chemical Company), hydroxypropyl cellulose (e.g., Klucel®, which may also be obtained from Dow), hydroxypropyl cellulose ethers (*see*, e.g., U.S. Patent No. 4,704,285 to Alderman), hydroxyethyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, ethyl cellulose, cellulose acetate phthalate, cellulose acetate butyrate, and the like. The carrier may also comprise two or more suitable polymers in combination, for example, a carbomer combined in an approximately 1:5 to 5:1 ratio, by weight, with a polyethylene oxide.

It is preferred that the present dosage unit contain only the active agents and the polymeric carrier. However, it may be desirable in some cases to include one or more additional components. For example, a lubricant may be included to facilitate the process of manufacturing the dosage units; lubricants may also optimize erosion rate and drug flux. If a lubricant is present, it will represent on the order of 0.01 wt.% to about 2 wt.%, preferably about 0.01 wt.% to 0.5 wt,%, of the dosage unit. Suitable lubricants include, but are not

9® and TWEEN-80®. Preferred dosage units of the invention, however, do not contain permeation enhancers.

Flavorings are not typically needed in the present drug dosage units, as the active agents do not, in general, have any taste. If for some reason a flavoring is desired, any suitable flavoring may be used, e.g., mannitol, lactose or artificial sweeteners such as aspartame. Coloring agents may be added, although again, such agents are not required. Examples of coloring agents include any of the water soluble FD&C dyes, mixtures of the same, or their corresponding lakes.

In addition, if desired, the present dosage units may be formulated with one or more preservatives or bacteriostatic agents, e.g., methyl hydroxybenzoate, propyl hydroxybenzoate, chlorocresol, benzalkonium chloride, or the like.

Also, one or more additional types of drugs, i.e., pharmacologically active agents other than androgenic agents, progestins and estrogens, may be incorporated into the present dosage units.

In general, the dosage unit of the invention is compositionally a substantially homogeneous, substantially uniform formulation. By "substantially uniform" is meant that the dosage unit is not coated, does not have a backing, and does not contain a plurality of layers or other types of discrete segments. Rather, the substance of the dosage unit is similar throughout, so that the unit is essentially "monolithic" in nature.

In another embodiment of the invention, a method is provided for administering a combination of steroidal agents using the buccal dosage units described hereinabove, containing an androgenic agent, a progestin, and an estrogen, or a progestin and an estrogen. The method generally comprises buccally administering the combination of active agents by affixing the dosage unit of the invention to the buccal mucosa of the individual and allowing the dosage unit to remain in place until erosion thereof--and thus drug delivery--is complete. Administration of a combination of steroidal active agents in this way is useful in a variety of contexts, as will be readily appreciated by those skilled in the art. For example, the buccal administration of the aforementioned combinations of steroidal agents may be used in female hormone replacement therapy, so that the symptoms or conditions resulting from altered hormone levels is mitigated or substantially prevented. As alluded to above, the method is also useful in other contexts, e.g., treatment of female sexual dysfunction, effecting female

urinary tract are improved. At the same time, the side effects normally expected and encountered with conventional hormone replacement are minimized or eliminated.

In treating female sexual dysfunction, and for the other indications described herein, the dosage and administration period will, again, vary depending on the individual and the severity of sexual dysfunction or other condition; however, in general, the preferred dosage and treatment regimen is as described above for hormone replacement therapy.

The buccal dosage units may be in the form of tablets made by either conventional compression or molding methods. *See, e.g., Remington's Pharmaceutical Sciences*, 18th edition (Easton, PA: Mack Publishing Co., 1990). Preferably, the dosage units are prepared by mixing the components together and compressing the mixture into tablet form. As will be appreciated by those skilled in the art, the erosion rate of the dosage unit, and thus the rate of drug delivery, is controlled by three factors: the pressure used to make the tablets, and thus the tablets' density; the carrier selected, as alluded to above; and the carrier-to-drug ratio. Pressure, carrier and carrier-to-drug ratio may thus be varied to obtain shorter acting or longer-lived dosage units.

The dosage units may have any of the conventional shapes, for example, lozenges, disks, wafers, tablets or the like. One possible configuration is a conventional tablet shape as shown in Figure 1, with the dosage unit indicated generally at **10**, the pharmaceutical composition *per se* shown at **12**, and the dosage unit's two parallel substantially planar surfaces shown at **14** and **16**; either surface can be used to affix the unit to the buccal mucosa. A more preferred configuration is shown in Figure 2, wherein the dosage unit is shown generally at **18** with the composition at **20**, and the two opposing concave surfaces at **22** and **24**; the opposing concave surfaces allow for a suction effect and improve adhesion of the unit to the mucosal tissue. It will be appreciated, of course, that only one of the two surfaces need be concave to achieve the desired suction effect. A less preferred configuration is shown in Figure 3, wherein the dosage unit shown generally at **26**, containing pharmaceutical composition **28**, has opposing convex surfaces **30** and **32**.

The dosage unit should have dimensions which fit conveniently into the buccal cavity, and, as emphasized elsewhere herein, is preferably quite compact. By way of example, suitable dimensions for the dosage unit are 2 mm to about 5 mm in diameter, preferably not exceeding about 5 mm in diameter, and about 0.3 to about 2 mm in thickness, preferably

examples which follow are intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

EXAMPLE 1

Buccal dosage units weighing approximately 10 mg each and containing testosterone, estradiol and progesterone as the active agents were prepared using a tablet direct press, as follows.

Tablet Composition

% BY WEIGHT	WEIGHT (mg)	COMPONENT
15%	1.5	Testosterone (USP, micronized, Pharmacia Upjohn)
3%	0.3	Estradiol (USP, micronized, Pharmacia Upjohn)
47%	4.7	Progesterone (USP, micronized, Pharmacia Upjohn)
24.8%	2.48	Polyethylene oxide (Polyox® WSR-303, Union Carbide)
10%	1.0	Carbomer (Carbopol® NF)
0.2%	0.02	Magnesium Stearate
100%	10.00 mg	

All components (i.e., testosterone, estradiol, polyethylene oxide, carbomer, and magnesium stearate, as set forth in the above table) were thoroughly mixed prior to tablet formation using aqueous fluid bed granulation to provide a homogeneous mixture of active agents and excipients. The individual dosage units were then made by applying 10 mg of the mixture into the punch die of the tablet press, and compressing the mixed components using a pressure in the range of approximately 500 to 2000 psi. Tablets having a diameter of

prepared. The tablets were removed from the punch die and the weight and dimensions of the tablets were measured.

EXAMPLE 3

Female patients in need of hormone replacement may be administered the buccal dosage unit described in Example 1 or Example 2 every 24-hour period. Plasma levels of androgen, progestin and estrogen are measured using conventional methodology, both prior to treatment and at intervals after the start of treatment. The change in steroid hormone levels prior to and following treatment may be used to assess the efficacy of the hormone supplement. Based on these measurements, a determination is made as to whether or not hormone levels have reached acceptable levels. The individuals' dosage may be adjusted accordingly.

EXAMPLE 4

Individual women are assessed and pre-screened to assemble an experimental group of subjects suffering from sexual dysfunction. The buccal drug dosage units of Examples 1 and 2 are each assessed in the experimental subjects for their ability to increase uterine or vaginal epithelial blood flow. Changes in blood flow or vaginal fluid production during and following buccal drug administration are determined using known methods. Increase in vaginal epithelial blood flow is determined using indirect methods such as photoplethysmography (Levin (1980) *Clinics in Obstet. Gynaecol.* 7:213-252), heated oxygen electrode (Wagner et al. (1978), "Vaginal Fluid" in *The Human Vagina*, Evans et al. (eds.), Amsterdam: Elsevier/North Holland Biomedical Press, pp. 121-137), and direct clearance of radioactive Xenon (Wagner et al. (1980) *Obstet. Gynaecol.* 56:621-624). Changes in vulvar blood flow are monitored using laser Doppler velocimetry (Sarrel (1990) *Obstet. Gynaecol.* 75:26S-32S).

Decreased vaginal dryness and/or dyspareunia are negatively correlated with vaginal blood flow rates, wherein increased blood flow to the vagina correlates with increased lubrication and decreased frequency and severity of dyspareunia (Sarrel (1990) *Obstet. Gynaecol.* 75:26S-32S). Accordingly, vulvar blood flow after treatment is assessed using laser Doppler velocimetry and compared to baseline levels. Increased vaginal lubrication as a

CLAIMS

1. A buccal dosage unit for administering a combination of steroidal active agents, comprising a compressed tablet of a bioerodible polymeric carrier and therapeutically effective amounts of an androgenic agent, a progestin and an estrogen.

2. The dosage unit of claim 1, wherein the androgenic agent is selected from the group consisting of androsterone, androsterone acetate, androsterone propionate, androsterone benzoate, androstenediol, androstenediol-3-acetate, androstenediol-17-acetate, androstenediol-3,17-diacetate, androstenediol-17-benzoate, androstenediol-3-acetate-17-benzoate, androstenedione, dehydro-epiandrosterone, sodium dehydroepiandrosterone sulfate, dromostanolone, dromostanolone propionate, ethylestrenol, fluoxymesterone, methyl testosterone, nandrolone phenpropionate, nandrolone decanoate, nandrolone furylpropionate, nandrolone cyclohexane-propionate, nandrolone benzoate, nandrolone cyclohexanecarboxylate, oxandrolone, oxymetholone, stanozolol, testosterone, 4-dihydrotestosterone, 5α-dihydrotestosterone, testolactone, pharmaceutically acceptable esters and salts thereof, and combinations of any of the foregoing.

3. The dosage unit of claim 2, wherein the androgenic agent is testosterone or a pharmaceutically acceptable ester thereof.

4. The dosage unit of claim 3, wherein the androgenic agent is a testosterone ester.

5. The dosage unit of claim 4, wherein the testosterone ester is selected from the group consisting of testosterone enanthate, propionate, cypionate, phenylacetate, acetate, buciclate, heptanoate, decanoate, undecanoate, caprate and isocaprate.

6. The dosage unit of claim 5, wherein the testosterone ester is selected from the group consisting of testosterone enanthate, propionate and cypionate.

7. The dosage unit of claim 3, wherein the androgenic agent is testosterone.

15. The dosage unit of claim 1, further including an effective amount of a lubricant.

16. A buccal dosage unit for administering a combination of steroidal active agents, comprising a compressed tablet of a bioerodible polymeric carrier and therapeutically effective amounts of a progestin and an estrogen.

17. The dosage unit of claim 16, wherein the progestin is selected from the group consisting of acetoxypregnenolone, allylestrenol, anagestone acetate, chlormadinone acetate, cyproterone, cyproterone acetate, desogestrel, dihydrogesterone, dimethisterone, ethisterone, ethynodiol diacetate, flurogestone acetate, gestadene. hydroxyprogesterone, hydroxyprogesterone acetate, hydroxyprogesterone caproate, hydroxymethylprogesterone, hydroxymethyl-progesterone acetate, 3-ketodesogestrel, levonorgestrel, lynestrenol, medrogestone, medroxyprogesterone acetate, megestrol, megestrol acetate, melengestrol acetate, norethindrone, norethindrone acetate, norethisterone, norethisterone acetate, norethynodrel, norgestimate, norgestrel, norgestrienone, normethisterone, progesterone, and combinations thereof.

18. The dosage unit of claim 17, wherein the progestin is selected from the group consisting of progesterone, cyproterone acetate, norethindrone, norethindrone acetate and levonorgestrel.

19. The dosage unit of claim 18, wherein the progestin is progesterone.

20. The dosage unit of any one of claims 16, 17, 18 and 19, wherein the estrogen is selected from the group consisting of 17α-estradiol, 17β-estradiol, ethynyl estradiol, pharmaceutically acceptable esters and ethers of 17α-estradiol, 17β-estradiol and ethynyl estradiol, estriol, estriol succinate, polyestrol phosphate, estrone, estrone acetate, estrone sulfate, piperazine estrone sulfate, quinestrol, mestranol and conjugated equine estrogens.

21. The dosage unit of claim 20, wherein the estrogen is 17β-estradiol or ethynyl estradiol.

33. A method for administering a combination of steroidal active agents to a female individual to achieve therapeutic blood levels thereof, comprising affixing the dosage unit of claims 1 or 16 to the buccal mucosa of the individual and allowing the dosage unit to remain in place until erosion thereof is complete.

34. A method for providing hormone replacement therapy to a female individual, comprising affixing the dosage unit of claims 1 or 16 to the buccal mucosa of the individual and allowing the dosage unit to remain in place until erosion thereof is complete.

35. A method for treating sexual dysfunction in a female individual, comprising buccally administering a combination of steroidal active agents to an individual in need of such treatment, wherein administration is carried out by affixing the dosage unit of claims 1 or 16 to the buccal mucosa of the individual and allowing the dosage unit to remain in place until erosion thereof is complete.

35. A method for facilitating transmucosal delivery of a combination of steroidal active agents to an individual which comprises affixing to the buccal mucosa of the individual the dosage unit of claims 1 or 16, and allowing the dosage unit to remain in place until erosion thereof is complete.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/01546

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61F 6/06

US CL : 424/430

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/430

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,543,154 A (RORK et al) 08 August 1996, see Abstract; column 4, lines 14-19; column 7, lines 26, and 36-41; column 8, lines 25-27.	1-35

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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Date of the actual completion of the international search	Date of mailing of the international search report
08 MARCH 2000	26 APR 2000
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